Engineering an L-cell line that expresses insulin under the control of the glucagon-like peptide-1 promoter for diabetes treatment.

ABSTRACT

Diabetes mellitus is a complicated disease with a pathophysiology that includes hyperinsulinemia, hyperglycemia and other metabolic impairments leading to many clinical complications. It is necessary to develop appropriate treatments to manage the disease and reduce possible acute and chronic side effects. The advent of gene therapy has generated excitement in the medical world for the possible application of gene therapy in the treatment of diabetes. The glucagon-like peptide-1 (GLP-1) promoter, which is recognised by gut L-cells, is an appealing candidate for gene therapy purposes. The specific properties of L-cells suggest that L-cells and the GLP-1 promoter would be useful for diabetes therapy approaches. Results: In this study, L-cells were isolated from a primary intestinal cell line to create suitable target cells for insulin expression studies. The isolated cells displayed L-cell properties and were therefore used as an L-cell surrogate. Next, the isolated L-cells were transfected with the recombinant plasmid consisting of an insulin gene located downstream of the GLP-1 promoter. The secretion tests revealed that an increase in glucose concentration from 5 mM to 25 mM induced insulin gene expression in the L-cells by 2.7-fold. Furthermore, L-cells quickly responded to the glucose stimulation; the amount of insulin protein increased 2-fold in the first 30 minutes and then reached a plateau after 90 minutes. Conclusion: Our data showed that L-cells efficiently produced the mature insulin protein. In addition, the insulin protein secretion was positively regulated with glucose induction. In conclusion, GLP-1 promoter and L-cell could be potential candidates for diabetes gene therapy agents.

Keyword: Clinical complications; Diabetes mellitus; Glucose concentration; Insulin gene; Intestinal cells; Isolated cells; Pathophysiology; Protein secretion; Recombinant plasmid; Side effect; Target cells.